REMARKS

Amendments

Claims 1-34, 51, 52 and 54-57 have been canceled, and claims 41-50 and 53 have been amended. Upon entry of the amendment, claims 41-50 and 53 will be pending. Support for the amendment can be found, for example, in Example 1.

The specification has been amended to update cited application information.

Rejections

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 40-50 and 53-57 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility for the reasons of record.

Applicant does not agree. Amended claim 53 is drawn to a transgenic mouse whose genome comprises a homozygous disruption in the gene encoding the mCAR2 protein, said protein comprising the amino acid sequence set forth in SEQ ID No:2; said mouse exhibiting, relative to a wild-type control mouse, lymphoid depletion of at least one the following: spleen, thymus and lymph nodes.

1. The Utility Requirement

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. This asserted utility is substantial, specific and credible.

Applicant directs the Examiner's attention to a recent NIH press release, wherein the NIH announced it was accessing Deltagen's data derived from its analysis of the mice:

> BETHESDA, Md., Wed., Oct. 5, 2005 - The National Institutes of Health (NIH) today announced contracts that will give researchers unprecedented access to two private collections of knockout mice, providing valuable models for the study of human disease and laying the groundwork for a public, genome-wide library of knockout mice.

Under terms of three-year contracts jointly funded by 19 NIH institutes, centers and offices, Deltagen Inc. of San Carlos, Calif., and Lexicon Genetics Incorporated of The Woodlands, Texas will provide NIH and its scientific partners with access to extensively characterized lines of mice in which a specific gene has been disrupted, or "knocked out." In the first year of the contract, NIH will expend about $10 million to acquire about 250 lines of knockout mice.

For each mouse line, the contractors will provide not only the mouse line itself, but also detailed, objective data on the impact of the specific gene deletion on the mouse's phenotype, which includes appearance, health, fitness, behavior, ability to reproduce, and radiological and microscopic data. Such comprehensive information on such a large group of mice has never been available to public sector researchers, and is expected to greatly accelerate efforts to explore gene functions in health and disease.

"Our decision to procure these knockout mouse lines and data and make them available to the research community will yield tremendous benefits, both in the short and long terms," said NIH Director Elias A. Zerhouni, M.D. "This trans-NIH initiative will place important mouse models into the hands of researchers, speeding advances in the understanding of human disease and the development of new therapies. It also represents a significant step in the direction of launching an international project to systematically knock out all genes in the mouse."

Since the early 1980s, when recombinant DNA technology was used to create the first such animals, knockout mice have proven to be one of the most powerful tools available to study the function of genes and to create mouse models of human disease. Researchers have produced knockout mice with characteristics similar to humans suffering from a wide range of disorders, including cancer, heart disease, neurological disorders and even obesity.

(See Researchers to Gain Wider Access to Knockout Mice Trans-NIH Effort Provides New Models for Understanding Human Disease; http://www.genome.gov/17015131) (copy attached).

Thus, the NIH regards the use of knockout mice obtained from Deltagen in studying gene function to be credible, substantial and specific.

With regard to commercial success, as argued previously, the invention has a substantial "real world use" as demonstrated by: (1) delivery of the claimed invention to at least one large pharmaceutical company (see Maglich *et al.*, *Mol. Pharm.* 62:638-646 (2002), Materials and Methods (copy attached)); and (2) commercial use of DeltaBase by three of the world's largest pharmaceutical companies, Merck, Pfizer and GlaxoSmithKline. DeltaBase incorporates the data set forth in the specification with regard to phenotypic analyses of the claimed mouse.

With respect to commercial use, the Federal Circuit has held:

> A correct finding of infringement of otherwise valid claims mandates as a matter of law a finding of utility under § 101. *See e.g., E.I. du Pont de Nemours & Co. v. Berkley & Co., supra,* 620 F.2d at 1258-61, 205 USPQ at 8-11; *Tapco Products Co. v. Van Mark Products Corp.*, 446 F.2d 420, 428, 170 USPQ 550, 555-56 (6th Cir.), *cert. denied*, 404 U.S. 986, 92 S. Ct. 451, 30 L. Ed. 2d 370 (1971). The rule is not related, as Raytheon argues, to whether a defendant may simultaneously assert non-utility and non-infringement; a defendant may do so. The rule relates to the time of decision not to the time of trial, and is but a *common sense approach to the law*. ***If a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established***. *People rarely, if ever, appropriate useless inventions*.
>
> Proof of such utility is further supported when, as here, the inventions set forth in [the] claims . . . have on their merits been met with commercial success.

Raytheon Co. v. Roper Corp. 724 F. 2d at 959; see also, *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1327, 6 U.S.P.Q.2d 1065 (D. Del. 1987), *affirmed*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989)); *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)(a patent system must be related to the world of commerce rather than to the realm of philosophy). See also, *In re Fisher* 76 U.S.P.Q. 2d 1225 (Fed. Cir. 2005)(Fisher did not present any evidence showing that agricultural companies have purchased or even expressed any interest in the claimed ESTs. And, it is entirely unclear from the record whether such business entities ever will.) Unlike *Fisher*, Applicant has submitted evidence that the claimed invention has been purchased and delivered to at least one large pharmaceutical company. Unlike *Fisher*, Appellant has presented evidence that the MCAR2 knockout mouse has actually been used in the real world.

As held by the Federal Circuit, common sense dictates that "[i]f a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established. People rarely, if ever, appropriate useless inventions." *Raytheon Co. at* 959. As people rarely, if ever, appropriate useless inventions, large pharmaceutical companies, rarely if ever, purchase useless inventions.

Thus, the Merck, Pfizer and GlaxoSmithKline regard the use of knockout mice obtained from Deltagen in studying gene function to be credible, substantial and specific.

Applicant respectfully submits that this evidence establishes the utility of the claimed invention.

2. Specific Utility

The Examiner continues to argue that the asserted use of studying gene function is not specific as "using the mice 'to study gene function' is so general as to be meaningless" (p. 20).

According to the MPEP, "specific utility" means "specific" to the subject matter claimed as compared to a "general utility" that would be applicable to the broad class of the invention (MPEP 2107.01). Use of the mCAR2 +/- and -/- mice to study the function of the mCAR2 gene and the association of the mCAR2 gene with, for example, thymic dysplasia and lymphocyte depletion, is specific to this mouse. Even if there were many other genes associated with these phenotypes, only the mCAR2 knockout mouse (as opposed to all other knockout mice) would be used to study the specific role of this gene. The Examiner is respectfully requested to explain (1) how the asserted utility of determining the function of the mCAR2 gene would be applicable to all other knockout mice; and (2) how the asserted use of studying the association of the mCAR2 gene with these phenotypes, would be applicable to all other knockout mice. The Examiner is requested to explain **how** all other knockout mice would be used to study the function of the MCAR2 gene.

3. Substantial Utility

The Examiner argues that "merely studying a gene using a knockout mouse is not a substantial 'real world use'" (p. 19).

As argued above, commercial use of the claimed invention clearly demonstrates a real-world, substantial use.

In addition, numerous post-filing date publication reveal that those skilled in the art are using the mouse to study the function of the CAR gene.

Maglich *et al.*, (cited above) discloses actual use of the claimed mouse as provided by Deltagen. GlaxoSmithKline reviewed data available thru DeltaBase and subsequently decide to order the mouse from Deltagen for additional analyses. Maglich notes that the CAR gene plays a central role in protecting the body against xenobiotics (abstract). As reported therein, "[i]n the current study, we have exploited PXR-and CAR-selective ligands as well as PXR- and CAR-null mice to examine systematically whether PXR and CAR regulate genes involved in the different

phases of xenobiotic metabolism in murine liver and small intestine and in human hepatocytes" (p. 639).

Wei *et al.*, *Nature* 407: 920-23 (2000)(copy of record) created a null CAR mouse "[t]o assess the functional role of CAR" (p. 921).

Ueda *et al.*, *Mol. Pharma.* 61:1-6 (2002)(copy attached) used null CAR mice to compare gene expression in wild type and knockout mice.

Huang *et al.*, *PNAS* 100:4156-61 (2003)(copy attached) used null CAR mice to study the role of CAR in bilirubin metabolism. (*See also*, Huang *et al.*, *J.Clin.Invest.* 113:137-143 (2004)(Huang et al., *Mol. Endo.* 18:2402-08 (2004)(copies attached)).

Zhang *et al.*, *J. Biol. Chem.* 279:49517-522 (2004)(copy attached) used null CAR mice to create a double knockout by crossing the null CAR mice with PXR null mice to "study their function in response to potentially toxic xenobiotic and endobiotic stimuli" (abstract).

Maglich *et al.*, *J. Biol. Chem.* 279:19832-838 (2004)(copy attached) "demonstrated that CAR plays a pivotal function in energy homeostasis and establish an unanticipated metabolic role for this nuclear receptor" (abstract). Again, the mice were provided to Glaxo by Deltagen.

Applicant submits that it cannot be reasonably argued that studying the function of the CAR gene is not substantial.

6. Additional Examiner Arguments

The Examiner argues that none of the asserted phenotypes correlate to a useful phenotype because the phenotypes are not specific to a disease (p. 6).

The issue is not whether the phenotypes are specific to a disease, but rather whether the asserted utility is specific to the claimed invention. Although not agreeing that there is any requirement that phenotypes be specific to a disease, Applicant submits that thymic dysplasia is a specific disease.

The Examiner argues that wild type mice could be used to identify agents (p.8).

Applicant respectfully submits that the Examiner's remark is irrelevant to the issue of utility of the claimed invention, as the standard is not a comparative or relative one. The claimed invention (CAR (-/-) mice) is the subject of the query, not wild-type mice.

The Examiner argues that the phenotypes may have been a result of the donating ES cell phenotype and cannot be compared to C57BL6 wild-type controls (p. 8).

The phenotypes were observed by comparing mCAR2 (-/-) mice with wild-type controls (+/+) of the same background (see Example 1, Table 1). It is well known in the art to compare knockouts with wild-type littermates. As exemplified in the attached Declaration of John Burke, the (-/-), (+/-) and (+/+) were all derived from the same ES cell line and are all of the same generation, F2N0. Thus, all of the mice upon which the observations were based are same background.

The Examiner cites Crabbe for the proposition that genetic background effects neurobehavioral phenotypes.

Crabbe relates to the effect of environment on the performance of multiple strains of inbred mice in several behavioral tests. Crabbe makes reference to certain strain-dependent behaviors in C57Bl/6 mice, but does not describe the effect of mixed strain or mutant strains on these behaviors, as suggested by the Examiner. More importantly, Crabbe does not make reference to strain-dependent effects on the presently claimed morphological phenotypes, particularly lymphoid depletion. Applicant is not claiming any behavioral phenotypes, and in particular is not claiming any phenotypes related to the behavioral parameters discussed in Crabbe. Applicant does not believe that Crabbe is sufficient to demonstrate that one skilled in the art would more likely than not doubt the asserted utility of the claimed mouse.

Applicant notes that none of the references cited by the Examiner demonstrates that genetic background has any effect on a phenotype of lymphoid depletion. As is standard in the art, Applicant compared the transgenic mice to wild-type control mice of the same ES cell line background, i.e. littermates. The Examiner has not presented any evidence that the 129 background contributed to the observed phenotype – i.e. no evidence has been presented that indicates that 129 mice exhibit any type of lymphoid depletion relative to the C57Bl/6 background strain. Therefore, the suggestion that the phenotype is a result of genetic background is unfounded.

The Examiner's remarks regarding Olsen and Bowery have been previously addressed. The Examiner has failed to respond to Applicant's response.

Strivastava fails to support the Examiner's position. The Examiner cites Strivastava for supporting that other genes or pathways can compensate for a knockout phenotype.

Strivastava describes a single knockout mouse (ANX7) and the phenotype exhibited by the heterozygous mouse. Strivastava proposes that the phenotype of defective β-cells is

compensated for by other pathways by increasing production of β-cells and loading of insulin into secretory granules in these cells. Despite this, Strivastava concludes that the ANX7 Ca2+ mediated GTPase functions in glucose dependent insulin secretion (see paragraph bridging p. 13787-13788). Contrary to the Examiner's characterization, Strivastava clearly does not support the position that knockout phenotypes do not reveal gene function, and would clearly consider the claimed mouse to be useful.

The Examiner argues that compounds that alter a phenotype may not be therapeutic in humans, citing MacDonald and Mombereau. Applicant is not claiming a method of treating a disease. The focus of the utility requirement is the claimed invention. Applicant is claiming a transgenic mouse, which is well-accepted as a tool useful for the determination of the function of the target gene and the study of observed phenotypes. Applicant has more than satisfied the burden with respect to the claimed transgenic mouse.

Furthermore, the teachings of MacDonald are not only irrelevant to the Examiner's position, but contradict it. First, MacDonald relates to use of a Kv2.1 antagonist to block glucose-dependent insulin secretion **in order to characterize the function of the Kv2.1 protein**. MacDonald takes no position on the utility of knockout mice, in particular for the purpose of identifying compounds. More importantly, MacDonald supports that antagonism of the Kv2.1 protein did reveal a function or role for the gene (see p. 44938 and throughout - "[t]he present study demonstrates an important role for Kv2.1 in ionic stimulus-secretion coupling of insulin secretion and reinforces the view that agents that enhance, but do not initiate, β-cell electrical activity by acting on Kv2.1 would be useful therapeutic agents, stimulating only postprandial insulin secretion."). MacDonald would clearly accept that *in vivo* antagonism of a target gene to determine gene function, such as by knockout of the gene, would be considered a credible utility.

Likewise, Mombereau fails to support a lack of utility of knockout mice. Mombereau studied the GABA-B1 knockout mice in various tests for anxiety and depression, and determined that the knockout mice exhibited increased anxiety and anti-depressant behavior. Mombereau confirmed the role of GABA-B1 in anxiety and depression by administering pharmacological agents that positively modulate or antagonize GABA-B1. Mombereau states that "these studies clearly demonstrate that GABA-B receptors play a role in the modulation of behaviors relevant to anxiety and depression" (p. 1058, first paragraph). Whether or not the agents identified or

used in such studies have been demonstrated to be capable of treating a human disease is entirely irrelevant to the issue of utility. Again, Applicant is not claiming a compound or a method for treating a human disease.

With regard to Austin and the NIH citation, the Examiner argues that the references were published well after the present application was filed.

The Applicant had previously responded to Examiner's remarks. However, the Examiner has not responded, but rather reiterates his previous position.

The Examiner argues that "nowhere has the applicant pointed to one piece of data that can be correlated to a disease state or that is capable of revealing the specific function of the mCAR2 gene" (p.19).

According to the specification:

> *Thymus*. Abnormalities in the thymus were detected, including reduced size and reduced weight of the thymus in mutant mice as compared to wild-type mice. Specifically, homozygous mice were reported to have small thymuses at necropsy as well as reduced thymus weights and reduced thymus to body weight ratio as compared to wild-type mice as shown in Figure 4 and the above Table 1.
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> Lymphoid depletion in the thymus was also detected. Specifically, reduction in the number of cortical lymphocytes and Hassall's corpuscles were reduced in number and were poorly formed. The changes seen in the thymuses were consistent with thymic dysplasia and severe atrophy. Thymic dysplasia, a congenital lesion associated with T cell immunodeficiency, consists variable degrees of the following features: a dramatic reduction in size of the thymus, a foliated appearance of the gland, depletion of lymphoid cells, and a lack of maturation of epithelial cells which appear primitive and fail to properly differentiate into Hassall's corpuscles. Thymic dysplasia may represent a failure or arrest in the embryological development of the gland. Atrophic changes of the thymus are acquired and can be induced by stress-related adrenocortical hyperactivity, decreased levels of growth hormone, and direct toxicity.

(Example 1). Thus, the specification clears set forth a specific disease and phenotypes correlated to the function of the mCAR2 gene.

The Examiner cites *Schoenwald* for the proposition that providing evidence that a product was known in the art was not evidence that the product had patentable utility.

Applicant previously responded to Examiner's remark. However, the Examiner has not responded to Applicant's arguments.

6. Summary

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying mCAR2 gene function with respect to the cited phenotypes, and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

An assertion of utility is credible unless the logic underlying the assertion is seriously flawed, or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (MPEP 2107.02, III(B)). The Examiner must provide evidence sufficient to show that the statement of asserted utility would be considered false by a person skilled in the art (MPEP 2107.02, III(A)). The Examiner has failed to provide any facts or reasoning sufficient to establish that a person of ordinary skill would not believe Applicant's assertion of utility.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly made a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant to be specific and substantial. (*In re Brana*; MPEP § 2107).

Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 40-50 and 53-57 have been rejected for lack of enablement, as the claimed invention allegedly lacks utility. As set forth above, it the Applicant's position the claimed invention satisfies the utility requirement and therefore one skilled in the art would clearly know how to use the invention.

Withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 112, 1st paragraph

Claim 40-50 and 53-57 and 53-57 stand rejected as allegedly failing to comply with the written description requirement.

The Examiner argues that "mCAR2" is new matter.

Applicant disagrees. According to the Federal Circuit:

The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that

the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language.

In re Kaslow, 707 F.2d 1366, 217 USPQ 1089 (Fed.Cir.1983). As amended, claim 53 is drawn to a mouse comprising a homozygous disruption in the gene encoding the mCAR2 protein. One skilled in the art would clearly recognize that the Applicant was in possession of a mouse having a disruption in the mCAR2 gene. The Examiner is respectfully requested to explain what "broad genus of any mCAR2 gene" he is referring to (page 22).

The phrase "null allele" has been deleted, without prejudice.

Withdrawal of the rejections is requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 40-50 and 53-57 stand rejected as allegedly indefinite.

The Examiner asserts that the term mCAR2 gene is indefinite.

As amended, claim 53 is drawn to a mouse having a homozygous disruption in the gene encoding the mCAR2 protein, said protein comprising the amino acid sequence set forth in SEQ ID No:2. One skilled in the art would clearly understand the meaning of the term.

Claims 41-50 have been rejected for allegedly being indefinite, specifically for recitation of "abnormality."

Applicant does not agree. In each instance, the term is modified by the location of the abnormality, by reference to a specific abnormality and by comparison with a wild-type control mouse. For example, claim 42 refers to a spleen abnormality comprising reduced spleen weight. The term would clearly be understood by one skilled in the art.

Applicant respectfully requests withdrawal of the rejections.

Rejection under 35 U.S.C. § 102(b)

Claims 39-50 and 53-57 stand rejected as anticipated by Kato, which is cited as disclosing a mouse having a disrupted VDR gene. The Examiner argues that the VDR gene "is a mCAR2 gene" because it shares homology with SEQ ID NO:1.

Applicant does not agree. As amended, claim 53 is drawn to a transgenic mouse whose genome comprises a homozygous disruption in the gene encoding the mCAR2 protein, said protein comprising the amino acid sequence set forth in SEQ ID No:2.

It would be clearly understood by one skilled in the art that the term refers to the mouse CAR gene. One skilled in the art would not agree with the Examiner that the VDR gene is the mCAR2 gene. Kato does not disclose the claimed mouse, and therefore does not anticipate the claimed invention. Withdrawal is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 53-57 stand rejected as allegedly being obvious over Kato supported by Li, in view of Choi, which is cited as disclosing SEQ ID NO:1. The Examiner argues that it would have been obvious to substitute the sequence disrupted by Kato with SEQ ID NO:1 to "gain clues" regarding the function of the mCAR2 allele.

Applicant respectfully traverses the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Applicant respectfully submits that the Office Action fails to establish a prima facie case of obviousness because there is no reasonable expectation of success to that which Applicant has done by modifying the cited references. Moreover, Applicant respectfully submits that the combination of the references fails to teach or suggest all the claimed subject matter.

As a preliminary matter, Applicant questions how the Examiner can argue that the requisite motivation exists to create the claimed subject matter, when the Examiner argues above that the claimed subject matter has no patentable utility and that one skilled in the art would not know how to use the claimed subject matter.

The cited references, neither alone or in combination, teach or suggest the presently claimed subject matter. There is no suggestion in either reference that one should substitute the disrupted VDR gene with the mCAR2 gene.

As amended, claim 53 is drawn to a transgenic mouse whose genome comprises a homozygous disruption in the gene encoding the mCAR2 protein, said protein comprising the amino acid sequence set forth in SEQ ID No:2; said mouse exhibiting, relative to a wild-type control mouse, lymphoid depletion of at least one the following: spleen, thymus and lymph

nodes. As acknowledged by the Examiner (page 26-27), the claim mouse having the recited phenotypes would not have been obvious at the time of invention.

Applicant respectfully requests the rejection be withdrawn.

In view of the above amendments and remarks, Applicant respectfully requests reconsideration and a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.

Respectfully submitted,

3-30-06

Date

John E. Burke, Reg. No. 35,836
Greenberg Traurig LLP
1200 17th Street, Suite 2400
Denver CO 80202
(303) 685-7411
(720) 904-6111 (fax)